UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte EMILIO BARBERA-GUILLEM

Appeal No. 2006-2466
Application No. 09/835,759

ON BRIEF

Before ADAMS, GRIMES, and LINCK, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This appeal involves claims to compositions comprising a tumor-associated antigen and a component that depletes B cells. The examiner has rejected the claims as anticipated and obvious. We have jurisdiction under 35 U.S.C. § 134. We affirm the obviousness rejection and reverse the anticipation rejection.

Background

"Primarily, there are two subsets of [CD4+ lymphocytes], TH1 cells and TH2 cells." Specification, page 1. TH1 cells "are generally accepted as being integral for cell mediated immunity" and TH2 cells "support a humoral immune response." Id., pages 1-2.

"In individuals (both animals and humans) bearing solid nonlymphoid tumors, tumor progression is associated with a change in the TH1/TH2 balance, in favor of a predominant TH2 response." Id., page 3. In fact, in these individuals, there may be a humoral immune response, referred to as "a pro-tumor immune response," that "has a propensity (e.g., as mediated through activated B cells, immune complexes, and activated immune effector cells) to: selectively drive the immune response, in polarizing the immune response, to comprise a TH2 response; preserve an immune response polarized to a TH2 response; and to suppress cell mediated immune response comprising a TH1 response (as exemplified by a TH2/TH1 imbalance)." Id., pages 21-22.

The specification describes vaccines and methods "to suppress a TH2 response, and induce a cell mediated immune response to tumor-associated antigen." Id., page 6. In particular, the specification describes "a vaccine comprising an immunotherapeutic composition, and tumor-associated antigen." Id., page 25. A "tumor-associated antigen" is "a composition comprising one or more antigens expressed by tumor cells of solid nonlymphoid tumor origin." Id., page 16.

An "immunotherapeutic composition" is "a composition (a) comprised of at least one affinity ligand which selectively (preferentially) binds to at least one determinant present on nonmalignant B cells, preferably mature B cells and/or memory B cells; and (b) where[ ]upon contact and binding to such B cells, directly or indirectly results in (causes and/or enables) B cell depletion when added in an amount effective to cause the B cell depletion." Id., pages 8-9. In reference to B cells, "depletion" means "one or more of: blocking of B cell function; functional inactivation of B cells; cytolysis of B cells;

inhibiting the proliferation of B cells; inhibiting the differentiation of B cells to plasma cells; causing a B cell dysfunction which results in an immunotherapeutic benefit; inhibiting secretion of cytokines or other tumor-promoting soluble factor(s) by activated B cells; [and] reduction in the number of B cells. . . ." Id., page 8. As an example, the specification states that "anti-CD22 mAb [monoclonal antibody] . . . may selectively bind to mature and/or memory B cells . . . and facilitate or result in B cell depletion." Id., page 9. The specification also states that the affinity ligand may be coupled to an anti-B cell agent, such as ricin A chain. Id., pages 9-10.

Discussion

1. Claim construction

Claims 1-5, 7-12, 69-73, 77, 78, 80-86, 90, 92-96, 100, 102-108, 112, 114, and 115 are pending and on appeal. Appellant has not separately argued any of the claims. Therefore, the claims stand or fall together. We will focus on claims 1 and 69, which are representative and read as follows:

> 1. A composition for treating a TH2 response and for inducing a cell mediated immune response comprising a TH1 response in an individual having a TH2/TH1 imbalance associated with a pro-tumor immune response, the composition comprising: an immunotherapeutic composition for effecting B cell depletion; and tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response.
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> 69. A composition comprising:
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> (a) an immunotherapeutic composition comprising a monoclonal antibody having binding specificity for CD22 for effecting B cell depletion; and
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> (b) tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response;
>
> wherein the composition is in an amount effective for suppressing a TH2 response, and for inducing a cell mediated immune response

comprising a TH1 response, in an individual having a TH2/TH1 imbalance associated with a pro-tumor immune response.

Thus, claim 1 is directed to a composition comprising: (a) "tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response" and (b) "an immunotherapeutic composition for effecting B cell depletion." The "immunotherapeutic composition" comprises an affinity ligand that selectively binds to a determinant present on nonmalignant B cells and, upon binding, directly or indirectly results in B cell depletion. Specification, pages 8-9.

Claim 69 is also directed to a composition comprising: (a) "tumor-associated antigen capable of inducing a cell mediated immune response comprising a TH1 response" and (b) "an immunotherapeutic composition for effecting B cell depletion." However, claim 69 recites "an immunotherapeutic composition comprising a monoclonal antibody having binding specificity for CD22" (emphasis added). In view of the "comprising" language, we interpret this limitation as encompassing immunotherapeutic compositions comprising an anti-CD22 mAb and another component, including a component that is coupled to the anti-CD22 mAb. We note that this interpretation is supported in the specification, which states that the affinity ligand of the immunotherapeutic composition may be coupled to an anti-B cell agent, such as ricin A chain. Page 10.

2. Anticipation

The examiner has rejected claims 1, 2, and 7-10 under 35 U.S.C. § 102(b) as anticipated by Noguchi,[1] as evidenced by page 11 of the specification and by Trinchieri.[2] The examiner argues that Noguchi teaches "a composition comprising a nonamer p53 peptide (234CM) (i.e., tumor-associated antigen) in QS-21 adjuvant, and IL-12, which is reasonably interpreted as an effector of B cell depletion," and that Trinchieri provides evidence that "IL-12 induces or promotes a TH1 response and inhibits a TH2 type or humoral/antibody response (see Figures 1 and 2)." Examiner's Answer, page 4.

Specifically, the examiner argues that "the claims are drawn to some unknown 'immunotherapeutic composition' identified solely by its principal biological activity, i.e., effecting B cell depletion. The specification defines B cell depletion broadly at page 8 . . . , which includes blocking of B cell function, inhibiting the proliferation of B cells, and inhibiting the differentiation of B cells to plasma cells." Examiner's Answer, page 6. The examiner argues that Figures 1 and 2 of Trinchieri "provide extrinsic evidence that IL-12 acts as a negative regulator of TH2 promoting cytokines, such as IL-5, which functions in the proliferation and differentiation of B cells." Id. Thus, the examiner argues that IL-12 "necessarily inhibit[s] B cell proliferation and differentiation" and is therefore "an effector of B cell depletion." Id., page 7.

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[1] Noguchi et al., "Influence of interleukin 12 on p53 peptide vaccination against established Meth A sarcoma," Proc. Natl. Acad. Sci USA., Vol. 92, pp. 2219-2223 (1995).
[2] Trinchieri, "Interleukin-12 and its role in the generation of T_H1 cells," Immunology Today, Vol. 14, No.7, pp. 335-338 (1993).

Appellant argues that Noguchi does not disclose all of the limitations of the claims. In particular, Appellant argues that IL-12 is not "an immunotherapeutic composition for effecting B cell depletion." Amended Appeal Brief, page 7.

We conclude that the examiner has not set forth a prima facie case that IL-12 is "an immunotherapeutic composition for effecting B cell depletion." As defined in the specification, an "immunotherapeutic composition" comprises an affinity ligand that selectively binds to a determinant present on nonmalignant B cells and, upon binding, directly or indirectly results in B cell depletion. Specification, pages 8-9. Regardless of whether IL-12 results in B cell depletion, the examiner did not present a prima facie case that IL-12 is an immunotherapeutic composition; i.e., that IL-12 comprises an affinity ligand that selectively binds to a determinant present on nonmalignant B cells. Therefore, the examiner has not presented a prima facie case that Noguchi anticipates claim 1 or claims 2 and 7-10, which depend from claim 1.

3. Obviousness

The examiner rejected claims 1-5, 7-12, 69-73, 77, 78, 80-86, 90, 92-96, 100, 102-108, 112, 114, and 115 under 35 U.S.C. § 103 as obvious over Apostolopoulos[3] in view of Tachibana,[4] Trinchieri, Parkhouse,[5] and Wang.[6] The examiner argues that Apostolopoulos teaches that "'mice immunized with either natural mucin (HMFG) or a 20mer synthetic peptide from the V[NT]R repeat or a MUC1 fusion protein (FP), and

[3] Apostolopoulos et al., "Cell-mediated immune responses to MUC1 fusion protein coupled to mannan," Vaccine, Vol. 14 No. 9, pp. 930-938 (1996).
[4] Tachibana et al., "Tumor Regression in Tumor-Bearing Mice by Inoculations of Immunogenic Somatic Hybrid Cells in Combination with Cyclophosphamide," Tokai J. Exp. Clin. Med., Vol. 8, No. 5, pp. 455-463 (1983).
[5] Parkhouse et al., "Two Surface Antigen Targets for Immunotoxin-Mediated Elimination of Normal and Neoplastic Murine B Cells," Current Topics in Microbiology & Immunology, Vol. 182, pp. 331-335 (1992).
[6] Wang, U.S. Patent No. 5,939,380, issued August 17, 1999.

challenged with MUC1^{+}3T3 cells, had poor tumor protection; significant antibody titers were produced, a detectable CD4^{+} DTH [delayed-type hypersensitivity], but no CTL [cytotoxic T cells] were found.' (see page 930, right column)." Examiner's Answer, page 11. In addition, Tachibana teaches that the "combined treatment with cyclophosphamide (an immunosuppressant to depress humoral response and/or regulatory cells; see page 456) plus hybrid cells showed no antibody elevation and immune complex production, but generation of potent cytotoxic T cells was comparable to that of immunized hosts and was followed by curative antitumor effect (see page 461)." Id., page 12. Furthermore, Parkhouse teaches "that normal B cells bear surface CD22 and an anti-CD22 antibody-ricin conjugate effectively depletes normal B cells (see Figure 3)." Id.

The examiner argues that, in view of the applied references, "one of ordinary skill in the art would have been motivated and had a reasonable expectation of success at the time the invention was made to . . . produce a composition . . . comprising a tumor-associated antigen (i.e., MUC1) and the anti-CD22 antibody-ricin conjugate of Parkhouse et al[.] for depleting B cells." Id., page 16. In particular, the examiner argues that:

> The motivation to make the above modifications is made explicit in the teachings of Apostolopoulos et al[.] who teach that induction of a humoral immune response (i.e., TH2 or antibody response) gives poor tumor protection accompanied by little cellular immunity and [that] induction of a cellular immune response (i.e., TH1 response) results in significant tumor protection, cytotoxic T lymphocytes and little antibody production (i.e., TH2 or humoral immune response) (see abstract). Additional motivation for the above modifications and in agreement with Apostolopoulos et al[.], Tachibana et al[.] state "[that] enhancement of tumor growth was caused by acceleration of humoral response existing beforehand in the tumor-bearing state" (see pg. 461). Therefore, one of

> ordinary skill in the art at the time the invention was made would have been motivated to shift the anti-tumor immune response from a humoral/antibody/TH2 immune response existing in the tumor-bearing state to a cellular/TH1 immune response using a composition comprising a B cell depleting agent as taught by Parkhouse et al[.] (i.e., anti-CD22 antibody-ricin conjugate) and a tumor-associated antigen (i.e., MUC1) capable of inducing a TH1 response for tumor therapy.

Id., page 17.

Appellant argues that none of Apostolopoulos, Tachibana, Trinchieri, or Wang "teach or suggest specifically depleting B cells and certainly do not teach or suggest depleting B cells with an anti-CD22 antibody" and that "[t]here is simply no motivation within Parkhouse, or in the other references, to make the combination proposed by the Patent Office." Amended Appeal Brief, page 11. In support of this position, Appellant notes that the "claims recite an anti-CD22 antibody to effect B cell depletion, while Parkhouse discloses an anti-CD22 antibody conjugated to the cellular toxin, ricin. Given the anti-CD22 antibody-ricin conjugate of Parkhouse, at best, it might have been obvious to try anti-CD22 antibody alone to see if B cells could be depleted." Id.

Appellant also argues that "there would have to be a reasonable expectation that modifying the anti-CD22-ricin conjugate to anti-CD22 without the conjugated ricin would be able to effect B cell depletion." Id. However, as noted by the examiner, the claims encompass an immunotherapeutic composition that comprises an anti-CD22 mAb and a component, such as ricin A chain, that is coupled to the anti-CD22 mAb. Thus, Appellant's arguments are not persuasive.

In addition, Appellant argues that "Apostolopoulos merely discloses that conjugation of tumor-specific antigens with certain carriers may facilitate a tumor-specific antigen in producing a cell mediated immune response rather than a humoral

immune response. There is no teaching or suggestion within Apostolopoulos that humoral immunity could or should be suppressed. There is no motivation to attempt to deplete B cells." Amended Appeal Brief, page 12. With regard to Tachibana, Appellant argues that "[d]isclosing that humoral immune responses inhibit cell mediated antitumor activity is not the same as disclosing or suggesting depletion of B cells or depletion of B cells with anti-CD22 antibody to eliminate a humoral immune response." Appellant also traverses the examiner's position that Apostolopoulos provides "explicit" motivation to combine, noting that Appellant was "unable to discover any mention in the cited passage pertaining to B cell depletion, let alone the reportedly explicit suggestion. Rather, to reach the conclusion urged by the Office requires a[n unsupported] leap that correlates inducing a cellular immune response (i.e., TH1) with depleting B cells." Reply Brief, page 4.

We conclude that the examiner has set forth a prima facie case of obviousness. As stated by Appellant, "Apostolopoulos discloses that administration of a tumor-associated antigen conjugated to a carbohydrate polymer (mannan) produced a cell mediated immune response that is effective against tumors, in contrast to previous reports where administration of this tumor-associated antigen, conjugated to carriers, produced a humoral immune response and ineffective antitumor activity." Amended Appeal Brief, page 9. As also stated by Appellant, "Tachibana discloses that induction of a tumor-specific humoral immune response in tumor-bearing mice, by administration of tumor-associated antigens in the context of tumor cell lines, caused enhancement of tumor growth . . . , [but,] when induction of humoral immunity was inhibited, through the use of the drug cyclophosphamide, that the enhanced tumor growth was not present."

Id. In fact, as stated by the examiner, Tachibana teaches that, with cyclophosphamide, "generation of potent cytotoxic T cells was comparable to that of immunized hosts and was followed by curative antitumor effect." Page 461.

Both Apostolopoulos and Tachibana teach that antitumor activity is associated with producing cellular rather than humoral immunity. Apostolopoulos, page 930, col. 2; Tachibana, page 461. In order to achieve this goal, Tachibana teaches administering the immunogenic hybrid cells with cyclophosphamide "as an immunosuppressant to depress humoral response . . . and/or regulatory cells." Id., page 456. In addition, Tachibana suggests that "humoral immune response existing beforehand in tumor-bearing mice was accelerated by inoculations of immunogenic hybrid cells and the resulting immune complexes interfere with cell-mediated immunity to cause enhancement of tumor growth." Id., page 458. Based on these teachings, we conclude that the examiner has set forth a prima facie case that it would have been obvious to administer a tumor-associated antigen with components other than cyclophosphamide that would depress the humoral response.

Parkhouse teaches that ricin-anti-CD22 conjugate depletes both normal and neoplastic B cells. Abstract. Specifically, Parkhouse describes anti-CD22 mAb coupled to ricin A chain. Page 333. As noted by the examiner, "B cells produce antibodies; antibodies mediate humoral immunity." Examiner's Answer, page 20. We agree with Appellant that "[d]isclosing that humoral immune responses inhibit cell mediated antitumor activity is not the same as disclosing or suggesting depletion of B cells or depletion of B cells with anti-CD22 antibody to eliminate a humoral immune response." However, because B cells produce the antibodies that mediate humoral immunity, we

conclude that the examiner has set forth a prima facie case that it would have been obvious to administer a tumor-associated antigen with ricin-anti-CD22 conjugate to depress humoral immunity.

In particular, we do not agree with Appellant's argument that "the conclusion urged by the Office requires a[n unsupported] leap that correlates inducing a cellular immune response (i.e., TH1) with depleting B cells." Instead, based on the teachings of Tachibana, we conclude that the obviousness rejection requires correlating depressing humoral immunity with depleting B cells. In addition, based on the known relationship between B cells and humoral immunity, we do not agree that this requires an unsupported leap. Thus, we conclude that the examiner has set forth a prima facie case of obviousness.

Summary

The examiner has not shown that the claims are anticipated. However, the examiner's obviousness rejection is supported by the preponderance of evidence. Therefore, we reverse the anticipation rejection, but affirm the obviousness rejection.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED

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Eric Grimes) BOARD OF PATENT
Administrative Patent Judge) APPEALS AND
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